UNCLASSIFIED

AD 295 730

Reproduced
by the

ARMED SERVICES TECHNICAL INFORMATION AGENCY
ARLINGTON HALL STATION
ARLINGTON 12, VIRGINIA

UNCLASSIFIED

NOTICE: When government or other drawings, specifications or other data are used for any purpose other than in connection with a definitely related government procurement operation, the U. S. Government thereby incurs no responsibility, nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use or sell any patented invention that may in any way be related thereto.

63-2-3

295 730

CATALOGED BY ASTIA
AD 295730

PROGRESS REPORT

Filed 1 January 1963

Dr. Charles G. Wilber
and
David Gardner

Kent State University
Kent, Ohio

The Stimulating Effect of Hexamethonium Bromide on Physical Performance

ASTIA
FEB 8 1963
TISIA

DA-49-193-MD-2216

Qualified requestors may obtain copies of the report from ASTIA

Unclassified

ABSTRACT

White, male, albino mice were used to test the effect of hexamethonium bromide on physical performance. The forced swimming test was the measure of physical performance. Doses less than about 42 mg/kg resulted in improved physical performance as indicated by swimming times which were as high as almost 700 percent of control. Doses above 42 mg/kg resulted in decreased swimming times. The possible mechanism of the effect is discussed.

INTRODUCTION

Hexamethonium bromide is classed as a ganglionic blocking agent. It is known by trivial designations C6 Bistrium Escmid Methium. In practical therapy it is said to be obsolete (1).

The drug is presumably a competative antagonist at the nerve endings in the ganglia. In this respect it is similar to the action of tubocurarine at the myoneural function, atropine at autonomic cholinergic nerve endings or dibenamine at autonomic adrenergic nerve endings (2). A detailed review of the pharmacology of methonium compounds has been published (3).

MATERIAL AND METHODS

Male albino mice weighing 20 25 grams each were used in these tests. Hexamethonium bromide was dissolved in mammalian physiological saline solution and injected intraperitoneally into the test mice. Control mice received an equal volume of saline solution. Concentrations of the drug were so pre pared that each animal received about 0.5 ml. of solution actual dosages varied from 0 to 50 mg per kg.

In order to measure effect of the drug on physical per formance test and control mice (5 minutes after injection)

were forced to swim in a water bath held at 25C. The procedure has been described previously (4, 5).

Swimming times were recorded to the nearest half minute. These values were rounded to the nearest minute for the final calculations.

RESULTS AND DISCUSSION

The results are summarized in Table 1. It is immediately clear that in low doses hexamethonium bromide has a stimulating effect on swimming time. All mice given doses of the drug up to 25 mg per kg showed greatly prolonged swimming times as compared with controls.

In order to illustrate the effect the results were plotted as in Figure 1. The dose was expressed logarithmically, the response as percent of control swimming time. It is evident that the resulting line cuts the control level (100 percent) at a dose value of about 42 mg/kg. This suggests that mice given a dose of about 42 mg/kg hexamethonium bromide should swim the same length of times as controls. Furthermore doses above that level clearly inhibit swimming, doses below that level stimulate swimming performance.

We ran a check of this interpolation to ascertain whether doses of about 42 mg/kg do in fact cause no significant

variation from control swimming times. Ten male albino mice were administered, intraperitoneally, doses of the drug which were nominally 42 mg/kg; calculation indicated that the mean dose was 39 mg/kg. The mice were forced to swim as previously described. The mean swimming time was equal to 130 percent of control--a value which checks rather well with our interpolation.

Moreover, if the line in Figure 1 is extrapolated to zero swimming, it crosses x- axis at dose equals about 65 mg/kg. One suggests that such a dose completely prevents muscular performance in mice. We did not check this extrapolation. A few mice given a dose of 75 mg/kg were unable to swim at all.

Of particular interest for our purposes is the pronounced improvement of maximum physical performance resulting from the use of this drug in mice. In view of the clear-cut results we now propose to study the effect of this agent in mice and in guinea pigs that have been exhausted or fatigued by forced physical performance.

The mechanism by which hexamethonium exerts its stimulating effect on physical performance in mice is obscure. The drug specifically antagonizes acetylcholine at the ganglionic synapse (3). The mode of action of the drug in pharmacological test preparations indicates that competition is the

key step. In some animals, the rabbit for example hexamethonium brings about pronounced peripheral vasodilation (6). If this obtains in mice treated with the agent it might suggest that better blood supply to the working muscles results from use of this drug.

In man, hexamethonium depresses sympathetic vasomotor tone resulting in an increased blood flow to the limbs. Such an action in mice would be of clear value in the improvement of physical performance.

In view of the fact that decreased swimming performance in rodents is correlated with high rates of change of blood lactic acid, of body temperature, and possibly of liver glycogen (5), any mechanism or agent which would reduce these rates of change should bring about improved swimming performance. The action of hexamethonium on the peripheral circulation is such as probably to reduce these rates of change.

The fact that large doses of hexamethonium induce central nervous depression is an adequate explanation for decreased physical performance after large doses.

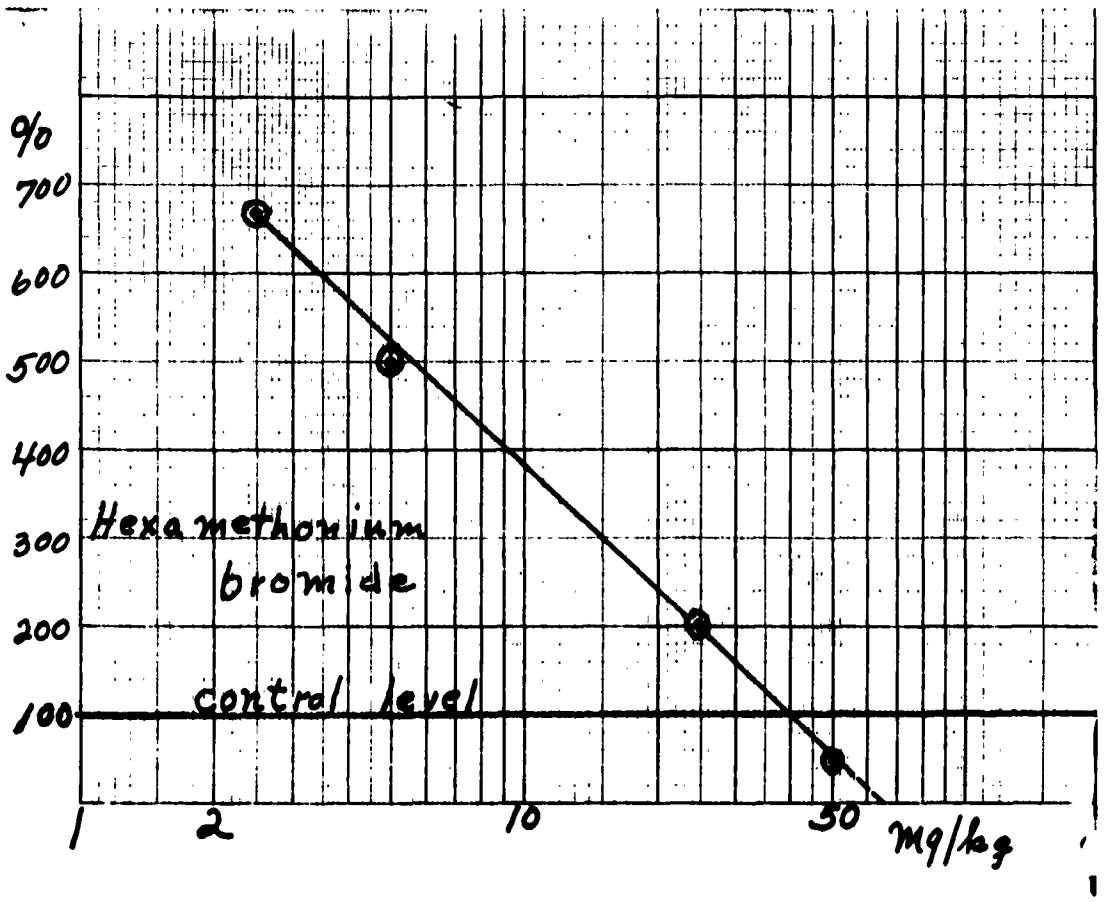
TABLE 1

The effect of various doses of hexamethonium bromide on swimming capacity of albino mice. Water temperature 24.5 ± 0.5C. Five animals used for each dose level. Standard deviations (S.D.) given for swimming times.

Dose in mg/kg	Mean swimming time (ST), minutes	S.D.	100/ST	ST as percent of control
0	16	2	6.25	100
2.5	108	9	0.92	675
5.0	75	0.1	1.33	500
25.0	33	3.0	3.03	206
50.0	8	2	12.50	50

FIGURE 1

Graph showing effects of hexamethonium bromide on swimming capacity in mice. Horizontal axis dose of drug in mg/kg on the logarithmic scale. Vertical axis, swimming time as percent of control on arithmetic scale. Θ, mean values for five animals; X, mean experimental check point to validate interpolation discussed in text. Dotted line, extrapolation of dose response curve to zero on the Y axis.


%
700
600
500
400
300
200
100
Hexamethonium
bromide
control level
1
2
10
30
mg/kg

REFERENCES

1. Cutting, W.C., 1962. Handbook of Pharmacology. Appleton Century Crafts. New York. 643p.

2. Lewis, J.L., 1960. An introduction to pharmacology. Livingston, Landon. 826p.

3. Paton, W.D.M. and Eleanor J. Zaimis, 1952. The methonium compounds. Pharmacol Rev. 4: 219-253.

4. Wilber, C.G. and J.B. Hunn 1960. Swimming of albino mice. J. Appl. Physiol. 15: 704-705.

5. Wilber, C.G., 1959. Some factors which are correlated with swimming capacity in guinea pigs. J. Appl. Physiol. 14: 199-203.

6. Wien, R. and D.F.J. Mason, 1951. Some actions of hexamethonium and certain analogues. Brit. J. Pharmacol. 6: 611-629.

STATEMENT OF COMMITMENT AND POLICY

All research done in these laboratories, in connection with the present project and all other projects which involve the use of animals, was carried out in strict accord with the letter and spirit of the following principles.

GUIDING PRINCIPLES IN THE CARE AND USE OF ANIMALS

(Approved by the Council of
The American Physiological Society)

Only animals that are lawfully acquired shall be used in this laboratory, and their retention and use shall be in every case in strict compliance with state and local laws and regulations.

Animals in the laboratory must receive every consideration for their bodily comfort, they must be kindly treated, properly fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during operative procedures. Where recovery from anesthesia is necessary during the study, acceptable technic to minimize pain must be followed. Curarizing agents are not anesthetics. Where the study does not require recovery from anesthesia, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain, and in any case shall be equivalent to accepted practices in schools of Veterinary Medicine.

When animals are used by students for their education or the advancement of science such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

Charles G. Wilber, Ph.D.
Dean of the Graduate School
and Professor of Physiology